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Synthesis of Amino Derivatives of Five-Membered Heterocycles by Thorpe–Ziegler Cyclization

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I. Introduction

One of the most convenient methods for the synthesis of functionalized amino heterocycles especially five-membered heteroaromatics (**4**), is the Thorpe–Ziegler cyclization (Scheme 1). A nitrile (**1**) undergoes ring closure by intramolecular addition of a deprotonated methylene group (EWG represents an electron-withdrawing group such as CN, COR′, COOR′, CONR′R″, NO_2, electron-deficient aryl, or heteroaryl) onto the cyano group followed by a 1,3-H shift in the intermediate **3**. There are two principal routes to precursors **1**: the introduction of a CH_2–EWG moiety by alkylation of compounds **5** and the substitution of a leaving group A in compounds **6** by $HZCH_2EWG$. Thorpe–Ziegler cyclizations are mostly catalyzed by bases, although acid catalysis (e.g., Vilsmeier conditions) have also been used. A num-

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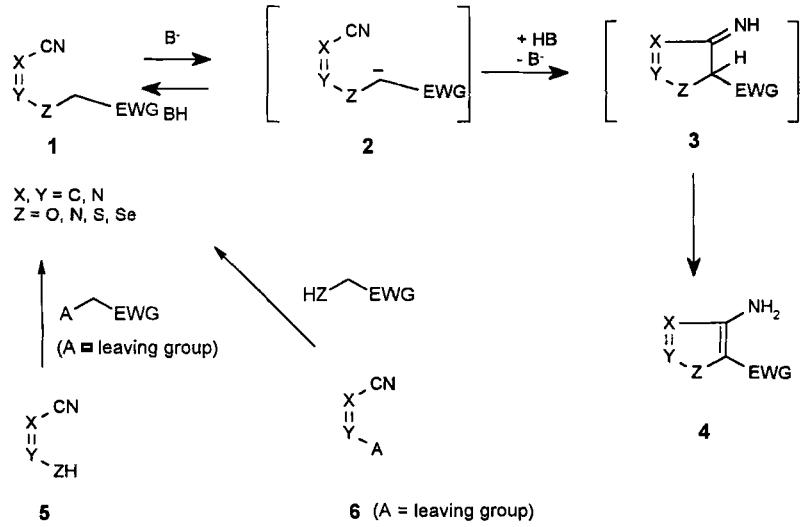


SCHEME 1

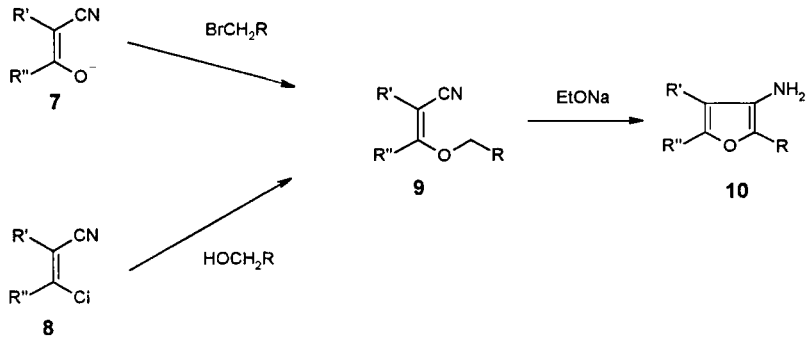
ber of reviews on Thorpe–Ziegler reactions have been published (67OR1; 70MI1; 80C101; 82MI1; 85MI1; 87MI1; 92MI1). Some are devoted to applications of the Thorpe–Ziegler reaction for synthesizing five-membered heterocycles (80C101; 85MI1). A recent review on 3-cyanopyridine-2(1*H*)-ones, -thiones and -selenones (92MI1) contains numerous examples of Thorpe–Ziegler syntheses of furo-, thieno-, and selenophenopyridines.

The present review covers the Thorpe–Ziegler syntheses of 3-aminofurans, 3-aminopyrroles, 3-aminothiophenes, 3-aminoselenophenes, and diverse aminoazoles as well as the corresponding annulated systems that appeared from 1983 to 1996 but excludes examples considered in the 3-cyanopyridine review (92MI1). Moreover, examples are included that do not report a separate Thorpe–Ziegler cyclization but are likely to involve this type of reaction (e.g., cases in which precursors **1** were not isolated and identified but directly formed in the reaction mixture). Special attention is paid to synthetic aspects, although some reaction mechanisms are discussed too.

II. Synthesis of 3-Aminofurans

A. Synthesis of Monocyclic 3-Aminofurans

Investigation of the cyclization of *O*-alkylated cyanoenols (**9**)[R′ = Ar, CN, R″ = Ar, H or R′R″ = $(CH_2)_4$] in the presence of sodium ethylate revealed (84LA1702) that acylmethyl substituents (R = Ar′CO or COMe)

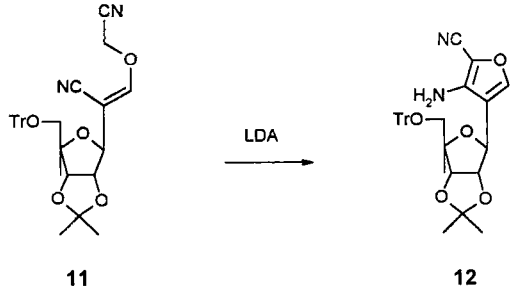


SCHEME 2

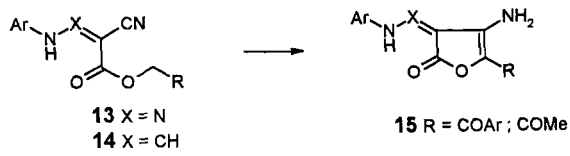
allowed a smooth Thorpe–Ziegler cyclization to 3-aminofurans (**10**), whereas less CH-acidic esters (**9**; R = COOEt, R′ = Ar) gave very poor yields and 4-nitrobenzylethers (**9**; R = 4-nitrophenyl, R′ = CN) resisted ring closure altogether. The starting materials (**9**) were accessible either from 3-hydroxyacrylonitriles (**7**) or from 3-chloroacrylonitriles (**8**) (Scheme 2).

Lithium diisopropyl amide (LDA) assisted Thorpe–Ziegler cyclization of cyanoenolethers (**11**) was used to synthesize the ribose-C-glycoside **12,** which was further transformed into a furo[3,2-*d*] pyrimidine (86TL815; 90MI1). Other bases such as NaOEt, 1,5-diazabicyclo[4,3,0] non-5-ene (DBN), *t*-BuOK or *n*-BuLi that were successfully used in pyrrole syntheses (see Section III.A) were not suitable for this furan formation (Scheme 3).

4-Aminofuran-2-ones (**15**) (R = COAr, COMe) could be synthesized by Thorpe–Ziegler cyclization of acylmethyl esters **13** and **14** in the presence of NEt_3 and NaOEt, respectively. However, the less acidic ethoxycarbonylmethyl componds **13** and **14** (R = COOEt) or cyanomethyl esters (R = CN) failed to ring close (84LA1702) (Scheme 4). The starting esters could



SCHEME 3

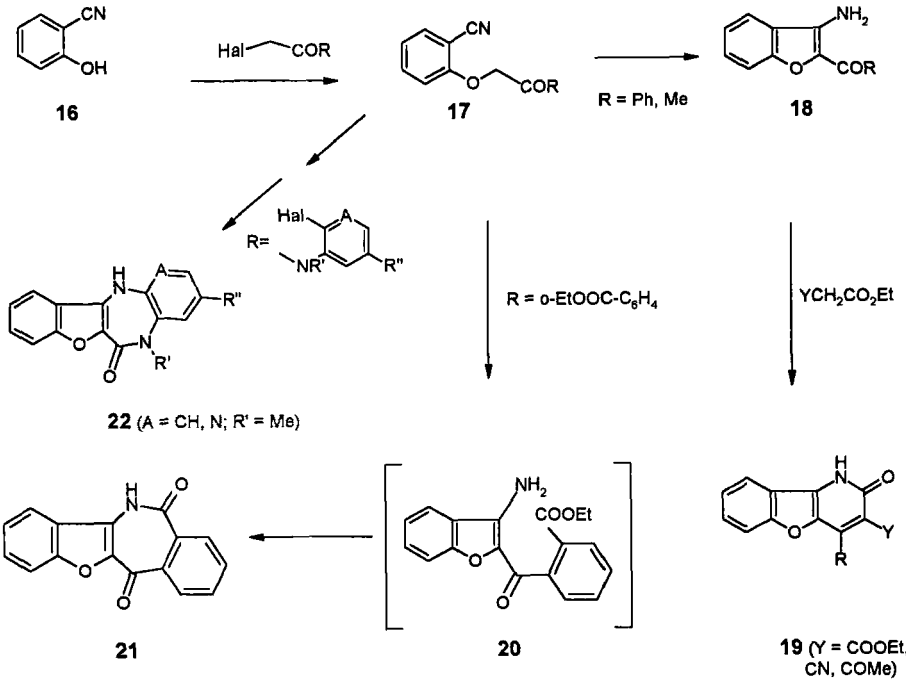


SCHEME 4

easily be obtained from corresponding acids and α-haloketones (R = COAr, COMe).

B. SYNTHESIS OF ANNULATED 3-AMINOFURANS

o-Cyanophenols are convenient starting compounds for the synthesis of 3-aminobenzofuran derivatives. Thus, *O*-alkylation of **16** followed by Thorpe–Ziegler cyclization of the intermediates **17** in the presence of K_2CO_3 smoothly yields the 2-acyl-3-aminobenzofurans **18**, which are the starting compounds for the synthesis of benzofuro[3,2-*b*] pyridines (**19**) [81IJC(B)391] (Scheme 5).



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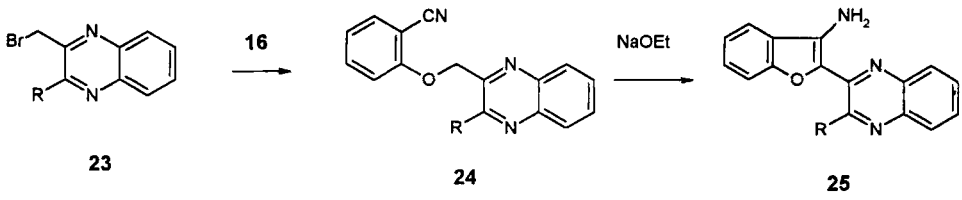


23 **24** **25**

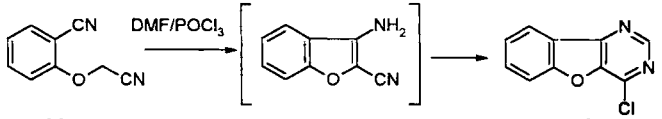
SCHEME 6

When ethyl *o*-bromoacetylbenzoate was used as an alkylating reagent in the presence of dimethylformamide (DMF) NaH, the expected Thorpe–Ziegler product (**20**) further cyclized to a condensed benzazepinedione (**21**) (91JHC379) whereas benzofurobenzodiazepinones (**22**) were obtained with aromatic haloacetamides (90JHC1369) (Scheme 5). It was claimed that quinoxaline rings were sufficiently electron withdrawing to enable a Thorpe–Ziegler cyclization affording 3-amino-2-quinoxalinyl-benzofuranes (**25**) (91EGP292001) (Scheme 6).

Interestingly, *o*-cyanomethoxybenzonitrile (**26**) gives a Thorpe–Ziegler type of cyclization under Vilsmeier conditions ($DMF/POCl_3$), that is without the addition of a base. Further cyclization of the assumed 3-amino-2-cyanobenzofuran **27** with the Vilsmeier reagent afforded benzofuro-[3,2-*d*]pyrimidine (**28**) in poor yield, (91JHC263) (Scheme 7).

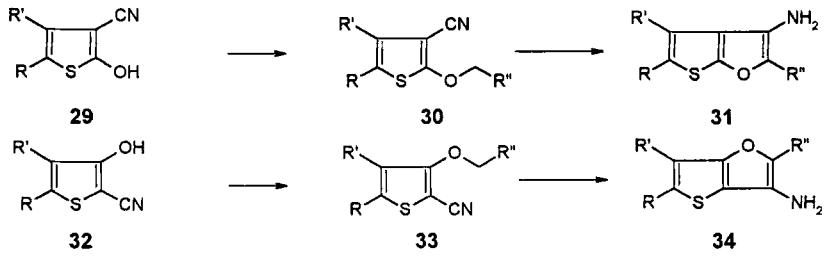
Thieno[2,3-*b*]furans (**31**) were obtained in modest yields (19–37%) starting from 2-hydroxy-3-cyanothiophenes (**29**) by *O*-alkylation with α-bromoketones or bromoacetate via Thorpe–Ziegler cyclization of the resulting ethers (**30**) in the presence of NaOEt (83JPR457). High yields (50–95%) were achieved with isomeric 2-cyano-3-hydroxythiophenes (**32**), affording thieno[3,2-*b*]furans **34** (83JPR457) (Scheme 8). The authors (83JPR457) attribute this difference in reactivity to the higher electrophilicity of the cyano group in intermediates (**30**) as compared with **33**.

Furo[3,2-*b*]benzothiophenes (**37**) were synthesized in an analogous way (91JHC269) by smooth cyclization of the cyanomethyl ether **36** in the presence of K_2CO_3/DMF. The starting 2-cyano-3-hydroxybenzothiophene **35** was obtained from methyl 2-thiohydroxybenzoate and chloroacetonitrile. Under Vilsmeier conditions ($POCl_3/DMF$), the 2-cyano-3-cyanomethoxy-



26 **27** **28**

SCHEME 7

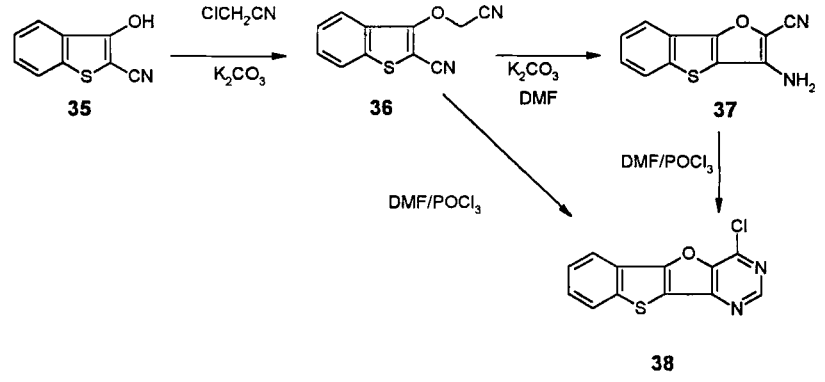


SCHEME 8

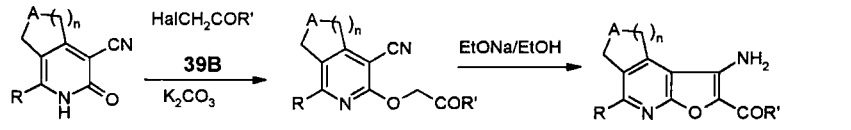
benzothiophene **36** also undergoes a Thorpe–Ziegler type of reaction, but further cyclization to the tetracyclic chloropyrimidine **38** was observed (91JHC269) (Scheme 9). The role that Vilsmeier conditions play in the mechanism of the Thorpe–Ziegler cyclization of **36** still remains unclear. Eventually intermediate 2-aza-3-chloro-propeniminium salts are formed by the addition of the formamide chloride to one of the cyano groups (88S655).

A great number of furo[2,3-*b*] pyridines were synthesized by *O*-alkylation of 3-cyano-pyridine-2-ones followed by base-catalyzed Thorpe–Ziegler cyclization of the resulting 2-alkoxy-3-cyanopyridines, which were often not isolated (82JPR933; 85MI2; 87IZV386; 89PS1; 92MI1; 95M945). For example, the interaction of condensed pyridine-2-ones (**39**) with halo carbonyl compounds followed by cyclization of **40** in the presence of EtONa afforded annulated aminofuropyridines (**41**) in high yields (82JPR933; 89PS1; 95M945) (Scheme 10). The latter can serve as starting materials for annulated pyrimidines (95M945).

The synthesis of the tetracyclic pyrido[3,2-*b*]furo [3,2-*b*]benzo[1,4]-diazepinone (**47**) starting with 2-cyano-3-hydroxypyridine (**42**) and 3-



SCHEME 9



39 (A = CH, S; n = O, 1) **40** **41** (R = Ph, OMe, NHPh, R' = Me, Ar, OEt, NHR")

SCHEME 10

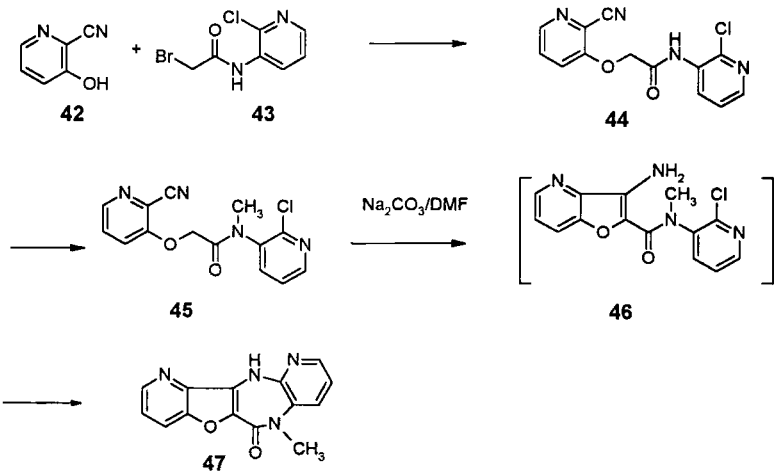
bromoacetylaminopyridine (**43**) also involves a Thorpe–Ziegler reaction, that is, formation of the aminofuropyridine **46**, which further forms a diazepine ring (Scheme 11). Because amide **44** resisted the base-catalyzed Thorpe–Ziegler cyclization, probably due to amide deprotonation, prior methylation of the amide was necessary (formation of **45**) (95H753).

Thorpe–Ziegler cyclization was further employed for the synthesis of aminofuro[2,3-*c*]pyridazine carboxylates (**50**) (90JPR104) and aminofurodibenz[*b,f*]azocines (**52**) (91KGS109) (Scheme 12).

III. Synthesis of 3-Aminopyrroles

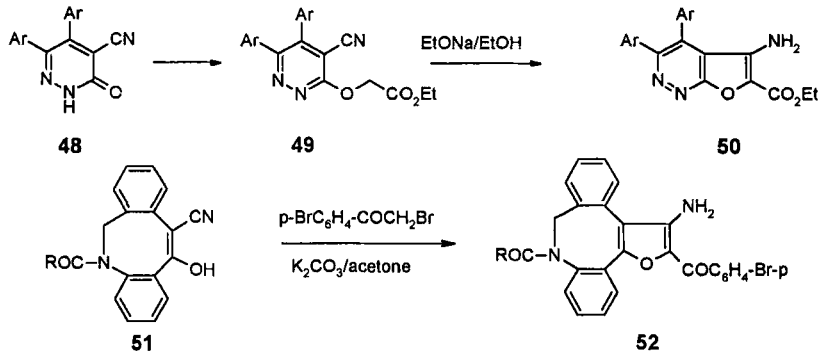
A. Synthesis of Monocyclic 3-Aminopyrroles

Thorpe–Ziegler cyclization of CH-acidic 3-aminocrotonitriles (**54**) was frequently used in the synthesis of 3-aminopyrroles (**55**) (Scheme 13). Usually this pyrrole formation proceeds more easily than the synthe-



42 **43** **44** **45** **46** **47**

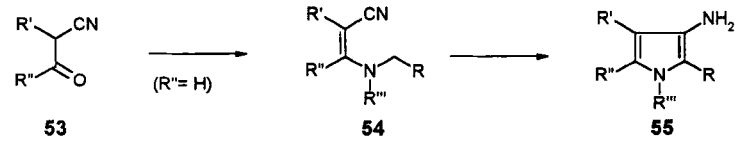
SCHEME 11



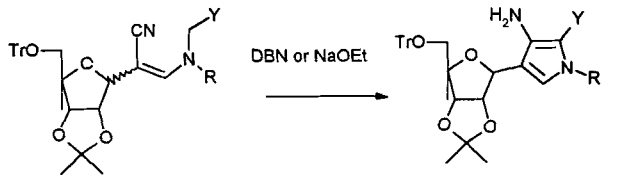
SCHEME 12

sis of analogous 3-aminofurane derivatives [see reference (86TL815)]. 3-Ethoxycarbonylmethylaminoacrylonitriles (**54**) (R″ = COOEt), available from the corresponding α-formylnitriles (**53**), afforded 3-aminopyrrole-2-carboxylates **55** (R″ = COOEt) in the presence of NaOEt or *t*-BuOK, which could further be transformed into pyrrolo[3,2-*d*]pyrimidines (79JOC3826). The yields of **55** strongly depend on the substituent R‴ attached to the nitrogen atom of **54**. Although secondary amino groups (R‴ = H) gave yields below 30%, better results (>90%) were achieved with tertiary amino groups (R‴ = alkyl) obtained by *N*-alkylation of **54** (R‴ = H) (Scheme 13). The authors explained this phenomenon by NH deprotonation when R‴ = H, thus preventing the CH deprotonation necessary for a successful Thorpe–Ziegler reaction. The same effects were observed in the synthesis of pyrrolo[3,2-*d*]pyrimidine C nucleosides (**57**) in which benzyl (R = Bn) (80TL1013) and ethoxycarbonyl (R = COOEt) (81TL25; 83JOC780) were used as N-blocking groups (Scheme 14). Similar blocking of the enamine NH group was applied to the preparation of 4-alkyl, 4-alkenyl, and 4-pyridylmethyl 3-aminopyrroles (**59**) as potential immunosuppressants (91USP4985433, 91USP4985434) (Scheme 15).

Substitution of one of the two alkylthio-leaving groups of bis-alkylthioacrylonitriles (**60**) by aminoacid derivatives yielded substituted enaminonitriles (**61**), which cyclized to 3-aminopyrroles (**62**) when heated in ethanol in the presence of triethylamine (88JPR1015) (Scheme 16).



SCHEME 13

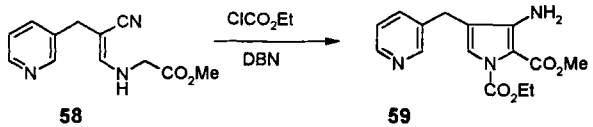


56 **57** (Y = CN, COOEt; R = Bn, COOEt)

SCHEME 14

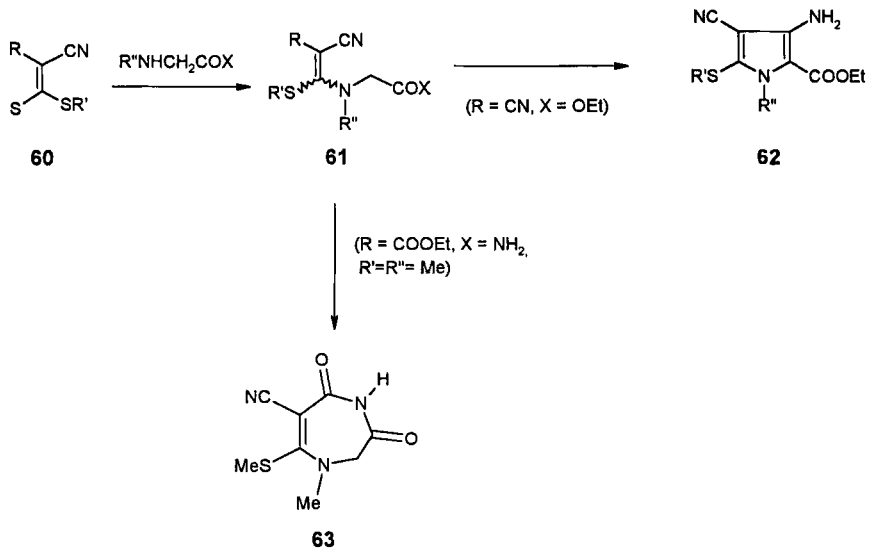
In contrast, the Thorpe–Ziegler cyclization failed with the glycine amide derivative **61** (X = NH_2, R = CN) (Scheme 16). In the opinion of the authors of the present review, this reluctance is likely caused by NH acidity rather than CH acidity as needed for Thorpe–Ziegler reactions. Interestingly, refluxing amide **61** (R′ = Me, X = NH_2, R = CO_2Et) in ethanol/Et_3N yielded the 1,4-diazepinedione **63** (88JPR1015). 3-Chloro and 3-ethoxyacrylonitriles (**64**) could be used as enaminonitrile precursors, directly affording 3-amino-pyrroles **65** in reactions with CH-acidic amines (93JPR491) in the presence of AcONa or Et_3N (Scheme 17). It is worth mentioning that the Thorpe–Ziegler cyclization to **65** proceeded smoothly even when R′ was H (ie, no blocking of the NH acidity was necessary). Possibly, the high electrophilicity of the intermediate malonic acid derivatives (**67**; R = electron withdrawing group) is responsible.

Another principal way to synthesize enaminonitriles (**67**) as precursors for Thorpe–Ziegler cyclizations to pyrroles (**65**) is the *N*-alkylation of enaminonitriles such as **66** (93JPR491). Intermediates **67** were isolated and cyclized to **65** in the presence of NaOEt (Scheme 17). When 2-cyano-3,3-diaminothioacrylanilide (**68**) was submitted to reactions with phenacyl bromides, the outcome depended on the conditions (Scheme 18). Triethylamine initiates an alkylation of the 3-amino group followed by Thorpe–Ziegler cyclization affording 2,4-diaminopyrroles **69.** In contrast, *S*-alkylation rather than *N*-alkylation took place when **68** reacted with phenacyl bromides in the presence of toluenesulfonic acid, leading to 1,4-thiazepines (**70**) (95JHC463, 95JHC1679) or to mixtures of **69** and **70.**



58 **59**

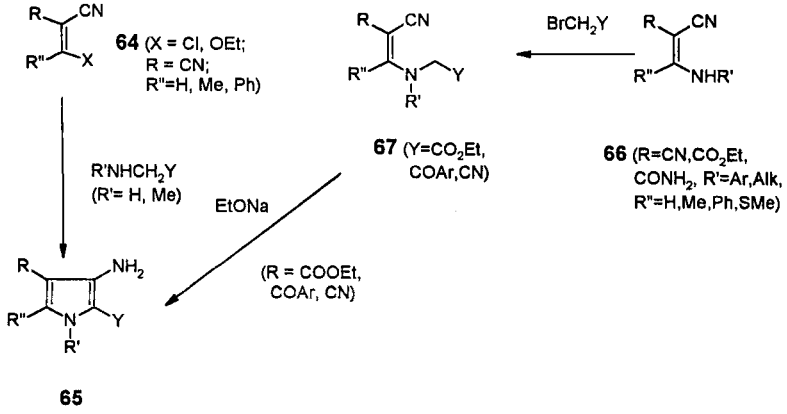
SCHEME 15



SCHEME 16

Interestingly, another type of cyclization occurred when 3-aminoacrylonitriles (**71**) were reacted with α-haloketones in DMF/K_2CO_3 (93JPR491). Alkylation of the 3-amino group was followed by substitution of the methylthio group by the carbonyl oxygen atom, affording oxazolines (**72**), which could also be ring transformed into Thorpe–Ziegler products **74** by ring opening (via **73**) in the presence of sodium alkoxides (Scheme 19).

3-Cyanomethylaminoenones or esters (**76**) (Scheme 20) can be consid-



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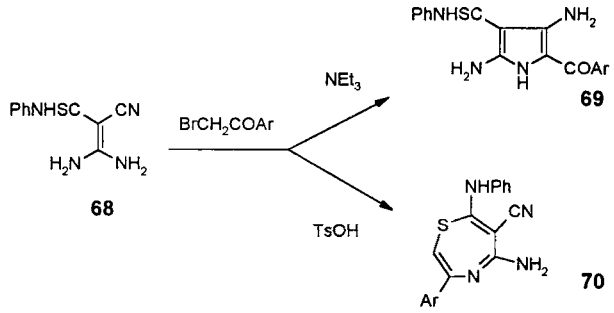


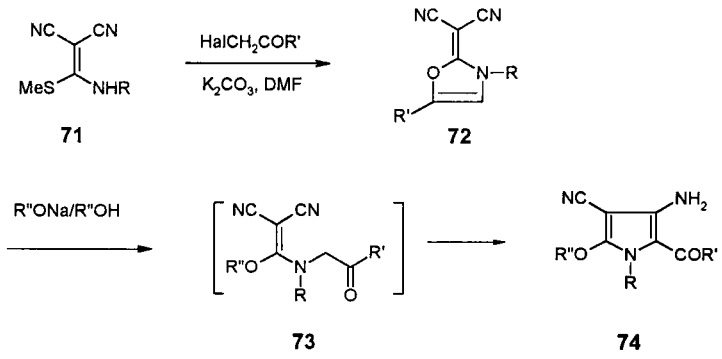
SCHEME 18

ered to be tautomers of precursors **1** (X = CH, Y = N, Z = CHMe) for Thorpe–Ziegler cyclizations (see Scheme 1). They could be obtained from the corresponding 1,3-dicarbonyl compounds (**75**) and afford (via **77**) intermediate 3-aminopyrroles (**78**), which condensed to bisethoxycarbonylvinylamino-pyrroles (**79**) and then intramolecularity cyclized into pyrrolopyridines (**80**) (85JHC83;90JHC120) (Scheme 20).

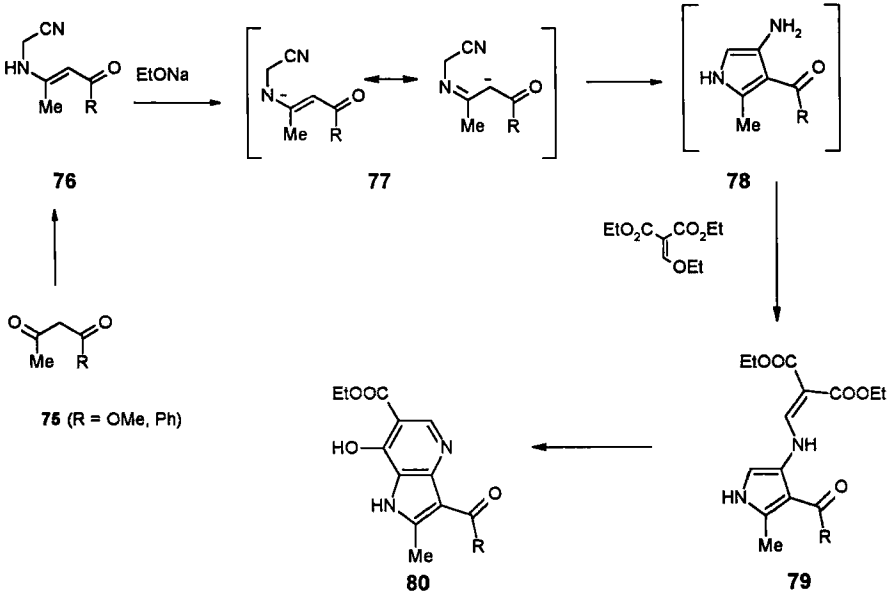
The formation of the 3H-3-morpholinopyrrole **82** from the cyanoazabutadiene **81** also involves a Thorpe–Ziegler type cyclization (Scheme 21) (for a further example in the tetrahydroindole series and the mechanism see Scheme 26) (87HCA187).

B. SYNTHESIS OF ANNULATED 3-AMINOPYRROLES

3-Aminopyrroles **85** (95HCA109) and **89** (93MC160; 96KFZ47) annullated with saturated carbocycles were synthesized from cyclic enaminonitriles **84** and **87** (formed from ketones **83, 86**), respectively (Schemes 22, 23).



SCHEME 19



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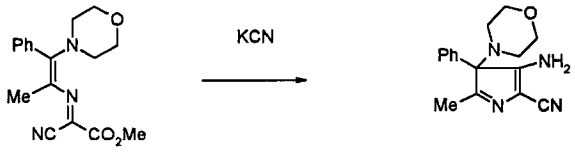

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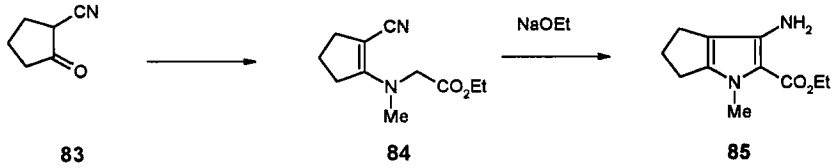
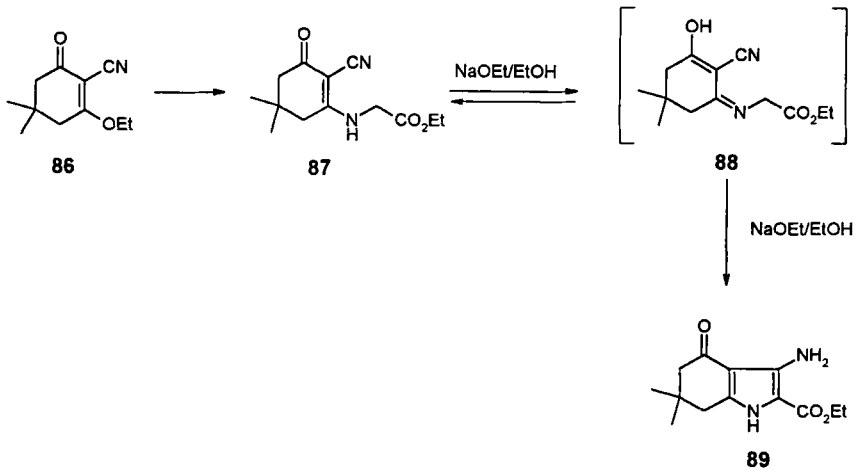
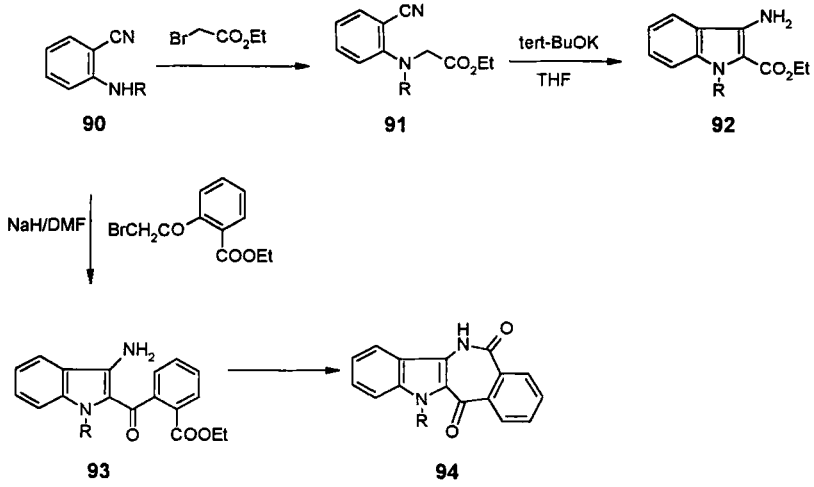


SCHEME 22

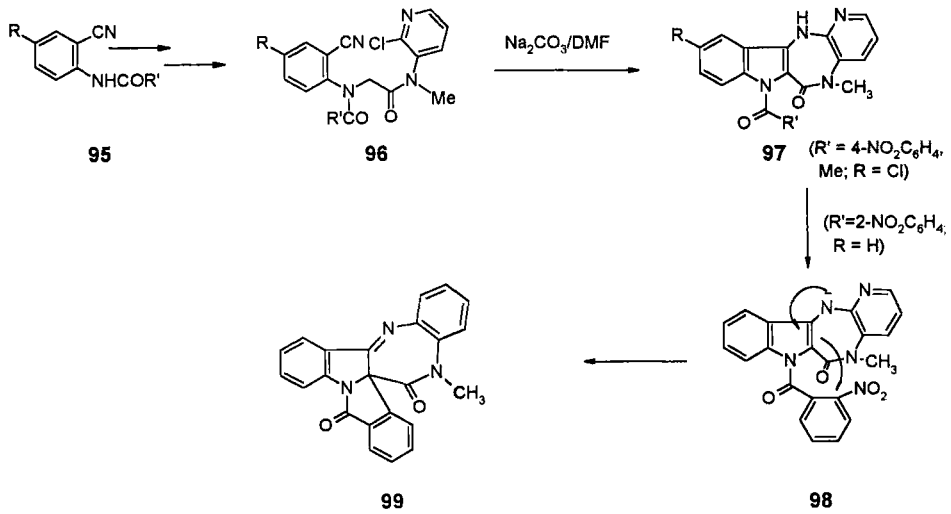


SCHEME 23

The smooth cyclization of the NH-acidic secondary enaminonitrile **87** was explained by intermediate rearrangement to the enol **88**, which is deprotonated at the NCH_2 group, allowing Thorpe–Ziegler cyclization (96KFZ47) (Scheme 23). In the aromatic indole series such as **92** (83JHC495), precursors **91** for Thorpe–Ziegler cyclization were synthesized by alkylation of the corresponding *o*-aminobenzonitriles (**90**). Modest yields were achieved regardless of the degree of N-substitution (R = H: 50%; R = Me: 22%) (Scheme 24).



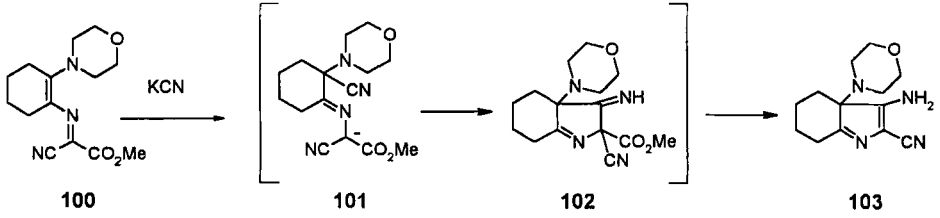
SCHEME 24



SCHEME 25

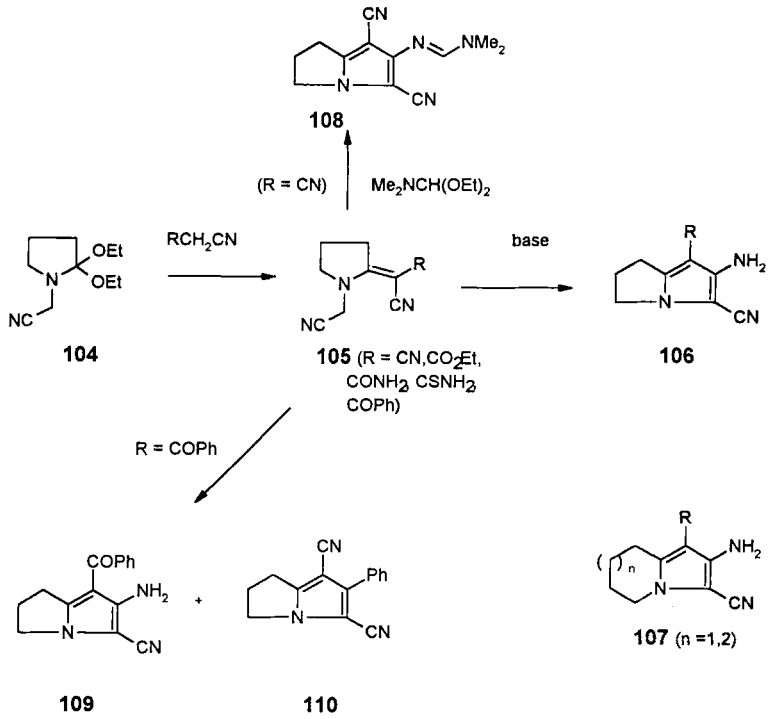
Thorpe–Ziegler synthesis of 3-aminoindoles with additional functional groups was used as part of the synthesis of condensed indoles [e.g., azepines (**94**) were obtained from 3-amino-2-benzoylindoles (**93**) (91JHC379) (Scheme 24)]. In these cases the nature of the substituent R is important for a smooth reaction (Ac < Bz < 2-NO_2-benzoyl, but no reaction when R = H). With 2-chloro-3-(*N*-bromoacetyl-*N*-methylamino)pyridine and *o*-benzoylaminobenzonitriles (**95**), the condensed pyridodiazepinones **97** and **99** (95H753) were obtained via intermediates **96** and 3-aminoindoles intermediate (via **98**) 3-aminoindoles followed by substitution of the 2-chloro substituent by the resulting 3-amino group (Scheme 25).

Scheme 26 represents a special case of a Thorpe–Ziegler cyclization (87HCA187). Cyanide is added to 5-(dialkylamino)-2-aza-1,3-diene-1-carbonitrile (**100**), generating an anion, (**101**) that undergoes a Thorpe–Ziegler cyclization. The resulting product (**102**) cannot give a proton shift but loses the COOMe moiety to generate the amino group in the product **103.**

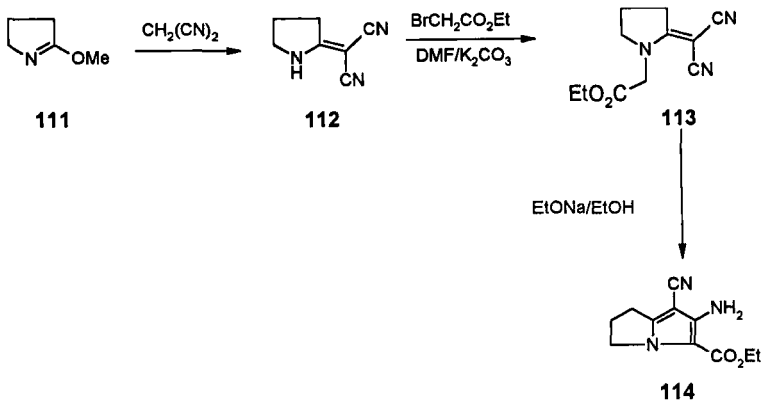


SCHEME 26

For other examples of the synthesis of annulated 3-aminoindole derivatives see Schäfer and Gewald (87JPR745). A number of investigations were allotted to the pyrrolizine synthesis by the Thorpe–Ziegler reaction. Thus, lactam acetal (**104**) could be condensed with acidic nitriles to give semicyclic enamino nitriles (**105**), which cyclized under basic conditions (e.g., 86KGS564; 87KGS1616; 87KFZ545, 90KFZ18; 91KFZ19, NaOEt), affording 3-amino-2-cyanopyrrolizines (**106**) (91KGS349; 94KFZ15) (Scheme 27). This method also was applied to the synthesis of pyrrolopyridines and pyrroloazepines (**107**) (94KFZ15) (Scheme 27). Thorpe–Ziegler reaction of enaminonitriles (**105**) was also possible in the presence of dimethylformamide diethylacetal, giving amidines (**108**) (87KGS1616) (Scheme 27). When ω-cyanoacetophenone was condensed with the lactam acetal **104,** the corresponding enamino nitrile **105** (R = COPh) was obtained as an *E*/*Z* mixture that cyclized to a 1:1 mixture of Thorpe–Ziegler product **109** and Dieckmann product **110** (91KFZ19) (Scheme 27).



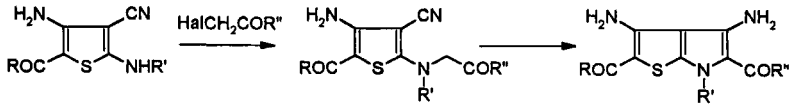
SCHEME 27



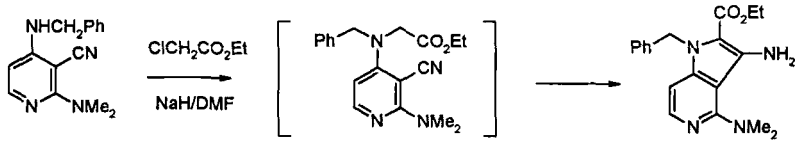
SCHEME 28

Another approach to the synthesis of pyrrolizines starts with the lactim ether **111**, which was condensed with malonodinitrile. The resulting enamino nitriles such as **112** were further *N*-alkylated with ethyl bromoacetate or phenacyl bromides, yielding intermediates such as **113,** which cyclize in the presence of NaOEt to the final products [e.g., **114** (90KFZ18; 91KFZ19) (Scheme 28)]. No intermediates were isolated when phase transfer catalysis was applied in the alkylation step. In a similar approach alkylation of an amino nitrile gave thieno[2,3-*b*]pyrroles (**117**) (Scheme 29) (86JPR459) and pyrrolo[3,2-*c*]pyridine (**120**) (Scheme 30) (95KFZ52) from 2-amino-3-cyanothiophenes (**115**) and the 4-amino-3-cyanopyridine **118**, respectively, and α-halocarbonyl compounds (117 and 120 are obtained according to Schemes 115–116 and 118–119, respectively).

The synthesis of pyrrolo[1,2-*a*]pyridines (**123**) starting from 1-benzyl-2-methylthiopyridinium salts (**121**) could be achieved by replacement of the 2-methylthio group by malononitrile and Thorpe–Ziegler cyclization (Scheme 31) (85JHC113). The CH-acidifying effect of aryl substituents was sufficient for the ring closure when LDA was used as a base. When 2-cyanomethylidenepyridines (**124**), structural analogs of **122,** were submitted to Diels–Alder cycloaddition with *N*-phenylmaleinimide prior to Thorpe–

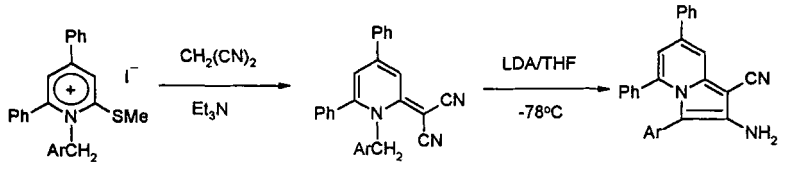


SCHEME 29



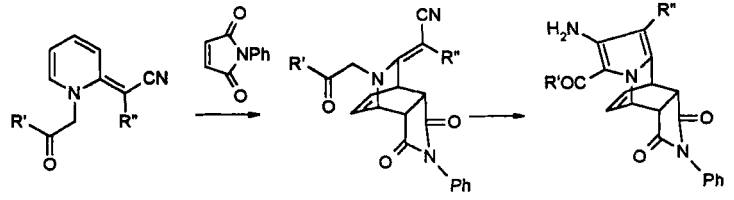
118 **119** **120**

SCHEME 30



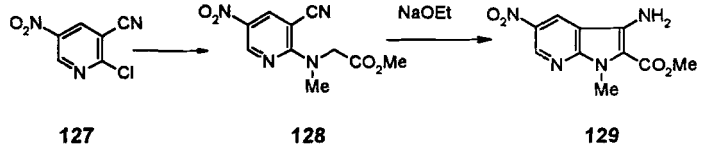
121 **122** **123**

SCHEME 31



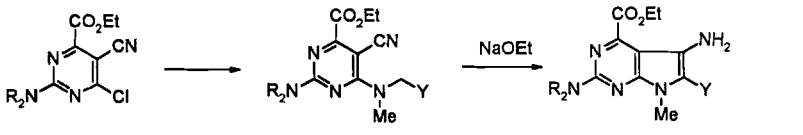
124 (R'=Me, OMe,OEt R"=CN,CO_2Me) **125** **126**

SCHEME 32



127 **128** **129**

SCHEME 33



130 **131** **132**

(Y = CN, CO_2Et; NR_2 = piperidino, morpholino)

SCHEME 34

Ziegler cyclization, interesting polycyclic aminopyrroles (**126**) (via intermediate **125**) were obtained [89H51; 92H(33)195] (Scheme 32).

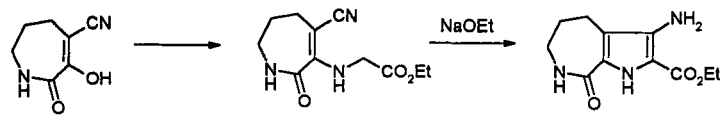
Substitution of chloride in *o*-chloronitriles **127** or **130** by glycine derivatives followed by Thorpe–Ziegler cyclization of the resulting *o*-aminonitrile structures was used to synthesize the 1-methyl-2-methoxycarbonyl-3-amino-5-nitro-pyrrolo[2,3-*b*]pyridine **129** (Scheme 33) (96KFZ36) and the pyrrolo[2,3-*d*]pyrimidines **132** (Scheme 34), (88LA633) respectively. Structural analogs of **128** with a hydrogen atom instead of a methyl group resisted cyclization. In spite of the presence of two acidic NH hydrogen atoms 3-amino-4-cyano-azepinone **134** underwent Thorpe–Ziegler cyclization to the pyrroloazepine **135** (80KGS109781TH1) (Scheme 35).

IV. Synthesis of 3-Aminothiophenes

There are numerous applications of the Thorpe–Ziegler reaction for the synthesis of thiophenes and annulated thiophenes. Only selected examples can be covered here. For more examples see reviews (85MI1; 86MI1; 92MI1).

A. Synthesis of Monocyclic 3-Aminothiophenes

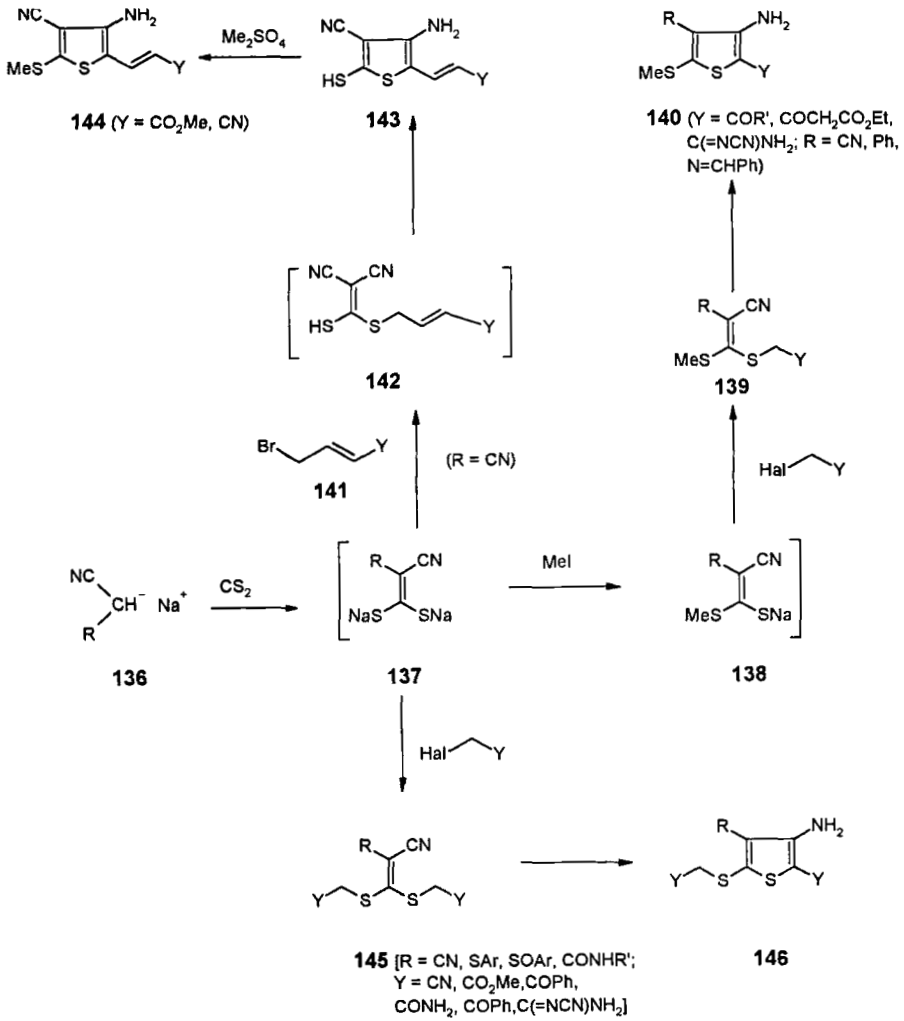
Ketene dithiolates (**137**), readily available from the corresponding substituted acetonitriles and carbon disulfide, serve as versatile starting materials for the synthesis of monocyclic 3-aminothiophenes (Scheme 36). Thus, one sulfur atom was methylated (formation of **138**); the other was alkylated



133 **134** **135**

SCHEME 35

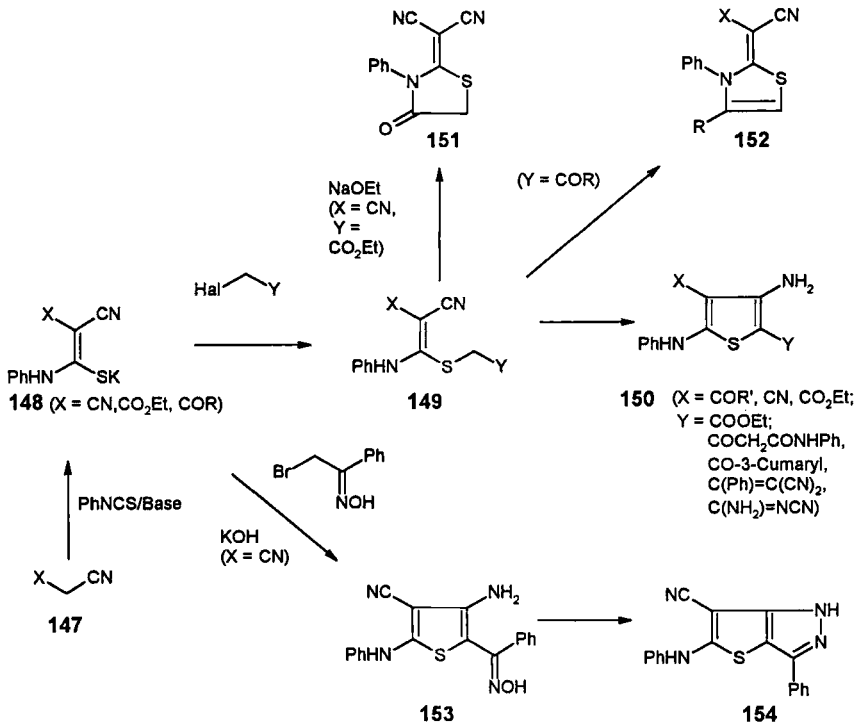
with a CH-acidic alkyl halide to **139**, allowing Thorpe–Ziegler cyclization to 3-amino-5-methylthiothiophenes (**140**) (83CPB2480; 84EGP206993, 84H697; 96T1011). The alkylation sequence could also be changed, that is, first introduction of the acidic alkyl substituent (with usage of **141**—formation of **142**) followed by Thorpe–Ziegler reaction to 3-amino-5-thiohydroxythiophenes (**143**) and final *S*-methylation, giving **144** (Scheme 36) (90LA115). Furthermore, both sulfur atoms of ketene dithiolates (**137**) could be *S*-alkylated by



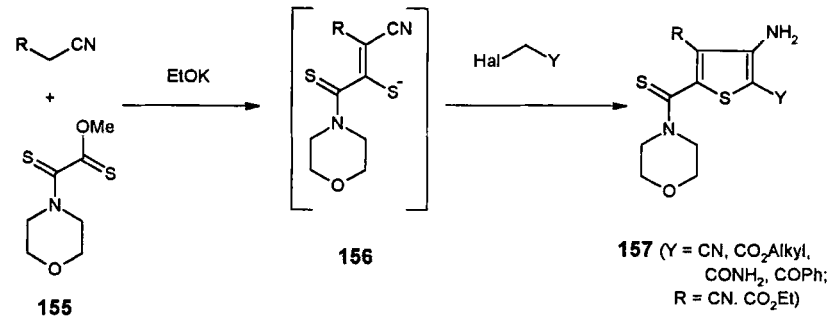
SCHEME 36

CH-acidic alkylating reagents, affording ketene dithioacetals (**145**), which underwent Thorpe–Ziegler cyclization to 3-aminothiophenes (**146**) (85BCJ2441; 86BCJ338; 89EGP265625; 92LA395; 94JHC771; 96T1011) (Scheme 36) or thieno[2,3-*b*]thiophenes (**176**) by twofold Thorpe–Ziegler cyclizations (see Section IV.B, Scheme 44).

Keten-*S*,*N*-acetals **148**, derived from the addition of acidic nitriles (**147**) to phenyl isothiocyanate [for an *in situ* method, see Mohareb (92M341)], were used for the synthesis of 2,4-diaminothiophenes such as **150** via the Thorpe–Ziegler reaction (Scheme 37) [86MI2; 91AP469; 92JCR(S)154; 92M341, 92MI2; 95ZOR127]. With α-haloketones or α-bromoesters an alternative cyclization was observed: Nucleophilic attack of the anilino substituent at the carbonyl group of the intermediate alkylation product **149** led to 1,3-thiazolidine-4-ones (**151**) (91AP469) or 1,3-thiazolines (**152**) (Scheme 37) [91AP469; 92JCR(S)154]. In some cases this problem could be circumvented by using α-bromooximes rather than ketones, affording corresponding oximes (**153**) of 2-benzoyl-3-aminothiophenes. The oximes (**153**) could be submitted to an interesting cyclocondensation to thienopy-



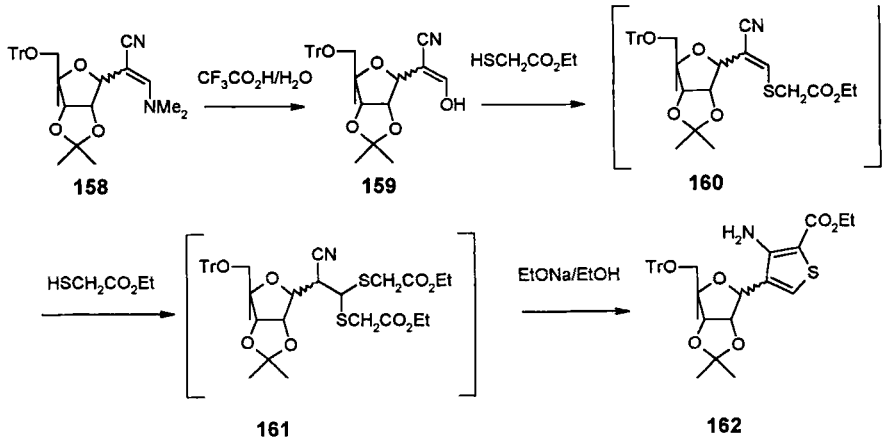
SCHEME 37



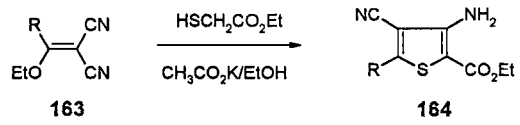
SCHEME 38

razoles (**154**) (91AP469) (Scheme 37). The dithiooxalester amide **155** was used to generate the 3-thiohydroxyacrylonitrile **156** by condensation, allowing the synthesis of 3-aminothiophenes (**157**) with a thioamide function in position 5 (87AP43) (Scheme 38).

Substituted 3-dimethylamino (**158**) and 3-alkylthioacrylonitrites (**160**) used as precursors for Thorpe–Ziegler cyclization to 3-aminothiophenes such as **162** (Scheme 39) (82JOC4633), **164** (Scheme 40) (82S1056), and **167** (Scheme 41) (84S275; 87PS351; 92M455) were obtained by substitution reactions with CH-acidic methyl thiols in which OH (**159**), EtO (**163**), or chloride (**165**) served as leaving groups in the starting acrylonitriles. The addition of a second molecule of thioglycolate (formation of **161**) in the course of the formation of the C-nucleoside **162** also took place (82JOC4633). The transforma-



SCHEME 39



163 **164**

SCHEME 40

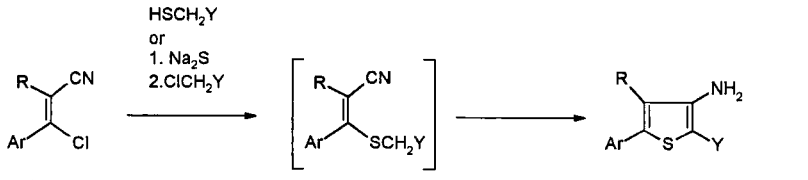
tion of 3-chlorocinnamonitriles (**165**) into 3-aminothiophenes (**167**) could alternatively be achieved by primary substitution of chloride by sulfide followed by *S*-alkylation and cyclization (92M455) (Scheme 41).

In addition to β-chloroacrylonitriles (**165**), α-chloroacrylonitriles (**168**) were used as starting material to make 3-aminothiophenes (**170**) (Scheme 42) [83JPR876; 89EUP298543; 92JAP(K)06/117, 263; 93 JCR(S)(2)72]. Intermediates **169** could be isolated and cyclized in a separate step (89EUP298543; 93JCR(S)(2)72; 94JAP(K)06, 25, 221). Furthermore, 2,3-dihalonitriles (**171**) were claimed to be starting materials for the preparation of 3-aminothiophenes (**170**) [92JAP(K)06/117, 263] (Scheme 42).

Finally, cyanoalkynes (**172**) also were used as precursors for 3-aminothiophenes (86JHC1757). Presumably, this synthesis starts with the addition of cyanomethylthiolate, affording intermediate β-cyanomethylthioacrylonitriles similar to **166** that finally undergo Thorpe–Ziegler cyclization to **173** (Scheme 43).

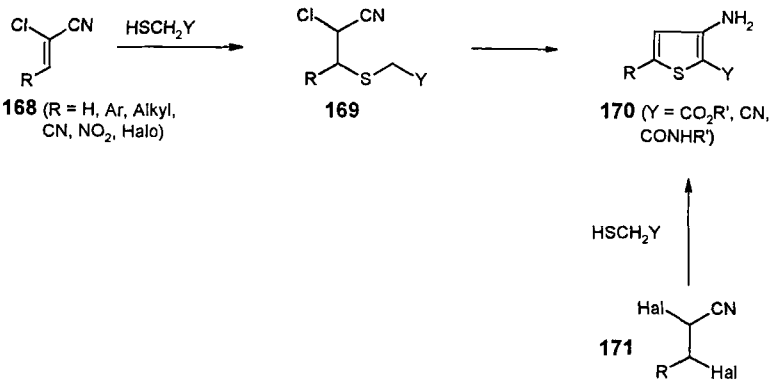
B. Synthesis of Annulated 3-Aminothiophenes

The synthetic approach to 3-aminothiophenes starting from ketene dithiolate (**174** ⟶ **175**) followed by Thorpe–Ziegler cyclization described in the previous section (see Scheme 36), was also applied to the synthesis of thieno[2,3-*b*]thiophenes (**176**) [Y = COR (85BCJ2441; 87MI2; 92PS15), CN (92PS15), CO_2Et (92PS15) CH=CHCN (90LA115), CH=CHCOOMe (90LA115), $C(NH_2)$=NCN (96T1011)] (Scheme 44). Two equivalents of



165 (R = H, CN) **166** **167**(Y = COAlkyl, COR', CHO, CN, NO_2)

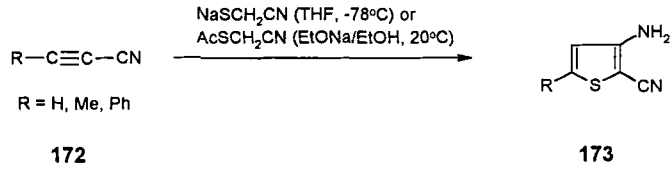
SCHEME 41



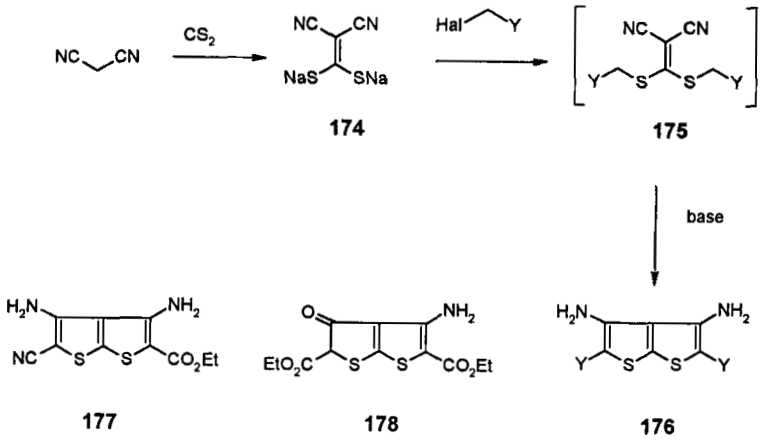
SCHEME 42

the CH-acidic alkylating reagent had to be used. By applying phase transfer catalysis and stepwise addition of different alkylating reagents, the asymmetrically substituted product **177** was obtained (92PS15) (Scheme 44). When ethyl cyanoacetate was used in place of malonodinitrile, Thorpe–Ziegler cyclization and Dieckmann cyclizations occurred after reaction with two equivalents of ethyl chloroacetate, affording mixtures of thieno[2,3-*b*]thiophenes **177** and **178** (92PS15).

In the synthesis of thieno[3,2-*d*]-1,2-thiazoles (**182**) (Scheme 45) (82AJC393), thieno[2,3-*d*]-1,3-dithioles (**186**) (Scheme 46) (87S655), and thienoazaindolizines (**189**) (Scheme 47) (90CPB2667) another strategy was applied: first preparation of a heterocycle bearing an *o*-thiohydroxynitrile or *o*-methylthiohydroxynitrile group and then formation of the thiophene ring by Thorpe–Ziegler cyclization. Thienoindolizines (**192**) (via **190, 191**) could be obtained in a similar way (Scheme 48), but due to the presence of two electrophilic groups (R′ = CN, R^1CO, CO_2Et) in positions 1 and 3 of the starting indolizine, a selectivity problem appeared. Thorpe–Ziegler cyclization or Dieckmann condensation could occur by way of these positions [87CL2043; 89BCJ119; 90CPB1527; 91JAP(K)03, 99081; 92CPB2313]. Based on quantum chemical calculations (89BCJ119; 92CPB2313) and ex-



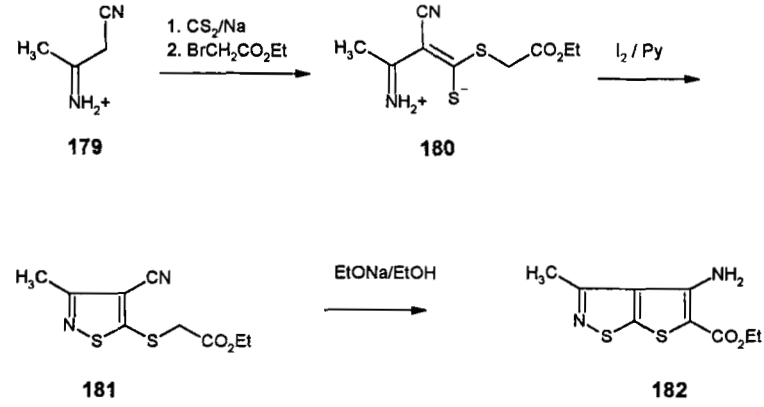
SCHEME 43



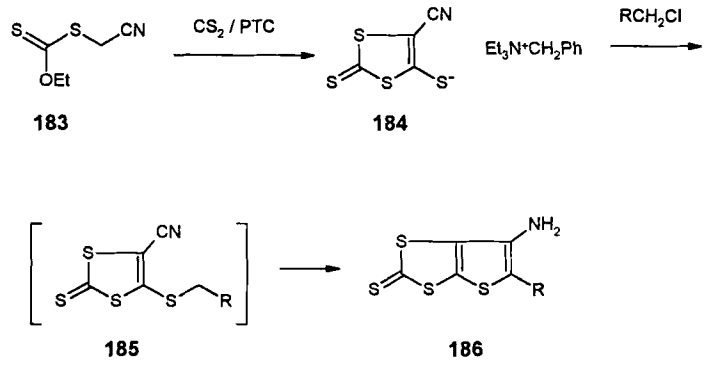
SCHEME 44

perimental data (87CL2043; 89BCJ119; 90CPB1527; 92CPB2313), the following order of reactivity of substituents in the desired Thorpe–Ziegler cyclization was determined: 3-CN > 1-CN > 3-keto > 3-ester > 1-ester. Thus, the substitution pattern shown in Scheme 48 gave unambiguously the Thorpe–Ziegler cyclization products **192.**

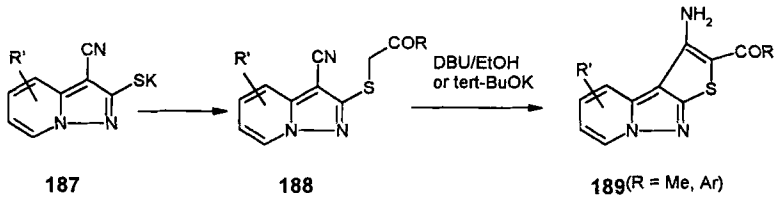
Alternatively, the acidic methylthio group was introduced by substitution of a suitable leaving group (OAlkyl, SMe, Halo, NO_2) in a cyanoheterocycle or cyanocarbocycle to obtain precursors for Thorpe–Ziegler cyclizations. In this way pyrrolo[4,3-*b*]thiophenes (**195**) (via **193, 194**) (Scheme 49) (88S449),



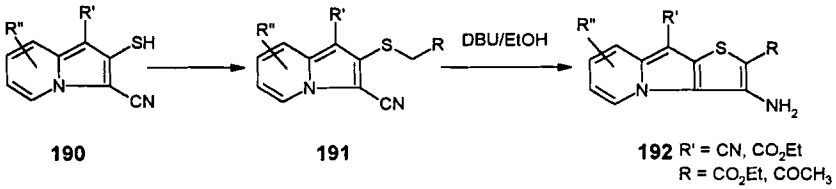
SCHEME 45



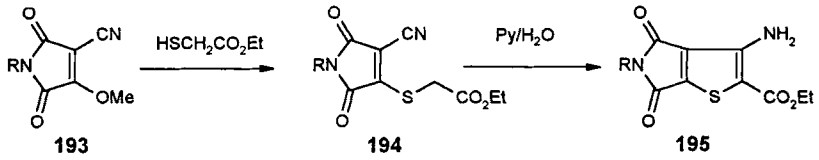
SCHEME 46



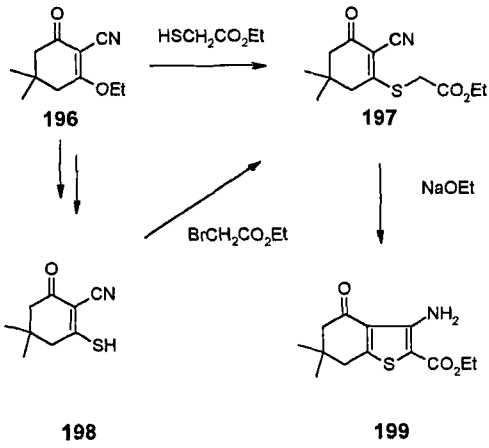
SCHEME 47



SCHEME 48

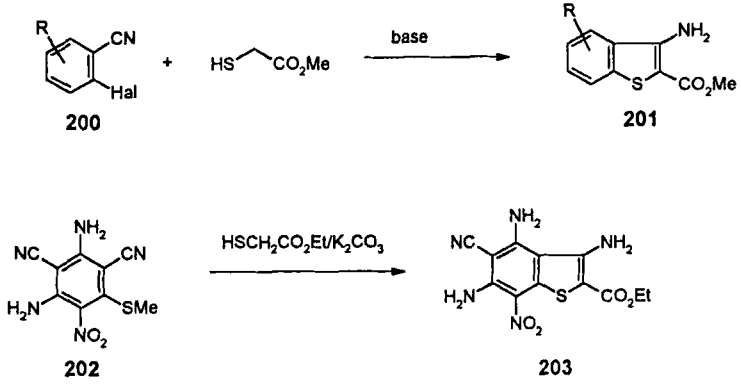


SCHEME 49

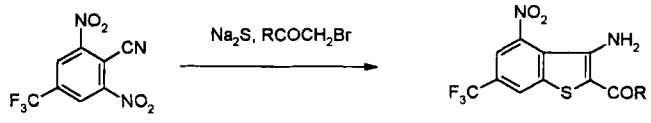


SCHEME 50

tetrahydrobenzo[*b*]thiophenes (**199**) (via **196–198**) (Scheme 50) (93MCI60), and benzo[*b*]thiophenes [**201** (via **200**) (Scheme 51) (80JHC1399; 92JMC2712) and **203** (from **202**) (Scheme 51) (85JPR328)] were obtained using thioglycolates as nucleophiles. This strategy was also followed in a stepwise way, first by thiolysis and subsequently by *S*-alkylation to synthesize the benzo[*b*]-thiophenes (**205**) (from **204**) (95MI1) (Scheme 52). In the syntheses of 3-aminobenzo[*b*]-thiophenes **210** (via **207, 208**) (Scheme 53) (81ZC183) and **213** (Scheme 54) (80LA768), precursors **209** and **212** were generated by Dimroth rearrangement of 2-aminothiopyranes (**206**) or by nucleophilic ring opening of benzoisothiazoles (**211**) respectively.



SCHEME 51

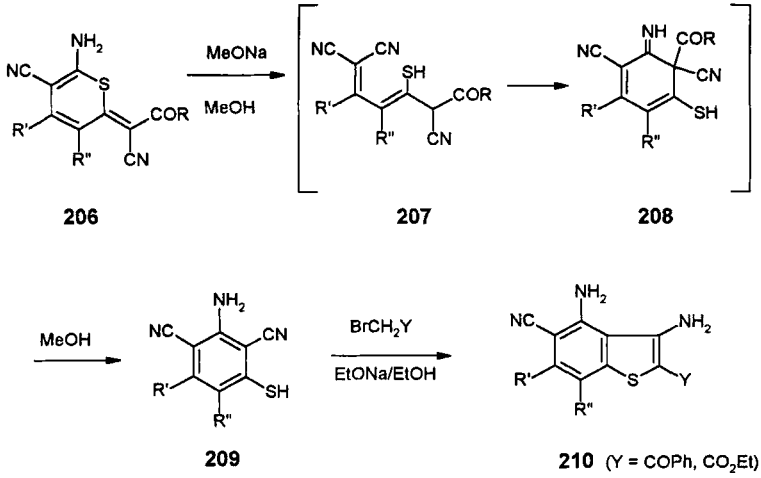


204 **205**

SCHEME 52

The formation of 3-amino-2-nitrobenzothiophene (**217**) (from **214**) by reaction of *o*-thiohydroxybenzonitrile and bromonitromethane looks like a normal Thorpe–Ziegler reaction [83JCS(CC)834; 86JCS(P1)1171] (Scheme 55). However, investigations of the mechanism revealed the formation of intermediate disulfides (**215**) rather than the expected *S*-alkylation products (**218**). The former are attacked at the cyano group by the nitromethane anion and close the thiophene ring by intramolecular disulfide cleavage (via **216**) [86JCS(P1)1171].

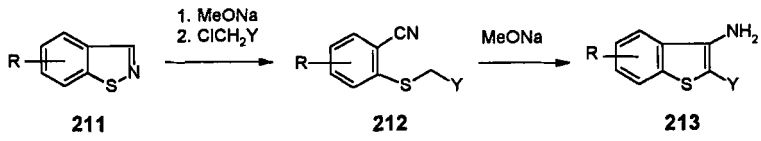
Thorpe–Ziegler cyclization is the most important route to thieno-[2,3-*b*]pyridines (**221**) (85MI1; 86MI1; 92MI1) (Scheme 56). Conveniently, the corresponding precursors (**220**) were obtained from pyridine-2-thiones (**219**) by *S*-alkylation in the presence of bases [89PS1; 92JCR(S)144; 95H753; 96KFZ36, 96T1011]. This approach has been widely used for the synthesis of numerous 3-cyanopyridine-2-thiones having alkyl and aryl substituents [86PHA827; 88KGS805; 89SUL47; 90MI2; 91PHA51, 91ZOB942; 92JPR483, 92KGS1280, 92PHA11; 93AP959, 93CCC1931, 93DOK97, 93JCR(S)(7)256, 93MI1, 93MC149; 96KGS59, 96KGS115], bearing func-



206 **207** **208**

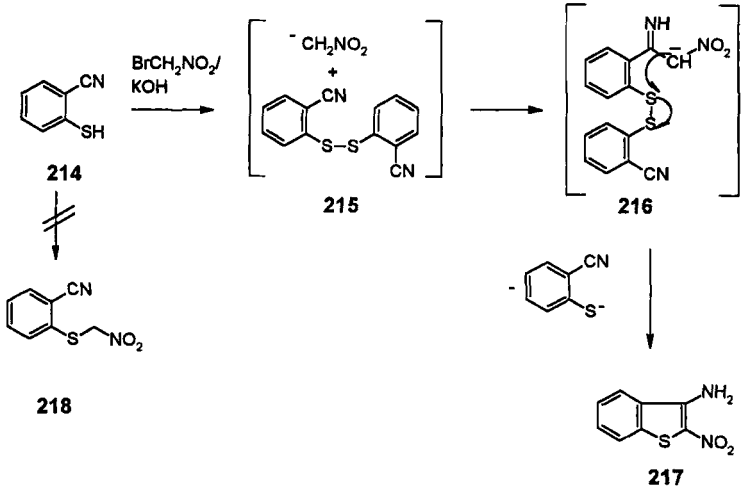
209 **210** (Y = COPh, CO_2Et)

SCHEME 53

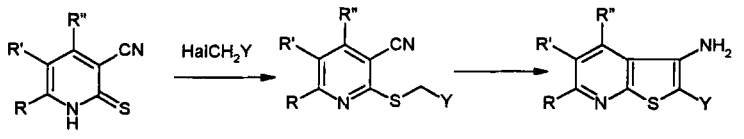


SCHEME 54

tional groups [89PS95; 90EGP275688, 90ZOB2384, 90ZOB2750; 91AP853, 91IZV1643, 91JCR(S)178, 91SL27, 91ZOB942; 92H(34)1721, 92JHC1693, 92KFZ62, 92MI3; 93BCJ555, 93LA1003; 94JCS(P1)1449, 94T6705, 94ZOR581], and being annulated to carbo- and heterocycles [85ZOB1656; 86ZOR1291; 88ZOR460; 89CS327; 91CCC1749, 91JCR(S)(5)116, 91PS (57)293, 91ZOR1996; 92BCJ2241; 93BCJ3716; 94KGS122; 95KGS250; 96KGS512], and for the synthesis of 3-cyano-1,4-dihydropyridine-2-thiones (87KGS124; 92KFZ40; 96KGS553). As shown in the 6-(pyrid-3-yl)-pyridine series (**222**) (Scheme 57) the ease of the cyclization step correlates with the chemical shift of the CH_2 protons of the precursor **220** in the ^1H NMR spectra and depends on the type of electron-withdrawing substituent Y (Y = COPh, CN, CO_2Et, $CONR^1_2$, COOH) (88KGS805). Appropriate reaction conditions were determined for different Y groups to match the CH acidity in these precursors. Thus, COOEt-substituted precursor **220** was found to be more reactive (MeONa as base) than the corresponding 4-nitrophenyl or 4-cyanophenyl derivatives (*t*-BuOK as base) in the formation of the thienopyridines (**223**; Y = CO_2Et, 4-$C_6H_4NO_2$, 4-C_6H_4CN) [91JCR(S)(7)178] (Scheme 57).



SCHEME 55



219 **220** **221**

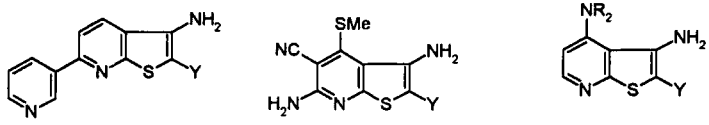
(Y = CN, COR^1, CO_2R^1, $CONR^1_2$, Aryl, NO_2, $C(NH_2)$=NCN...)

SCHEME 56

Other substituents in the precursors **220** may also influence the cyclization tendency to thienopyridines (**221**) (93MC149) (Scheme 56). Thus, an intermediate (**220**) could be isolated during the synthesis of diaminothieno[2,3-*b*]pyridines (**224**) (Y = $CONR^1_2$) when NR_2 was NMe_2, whereas the corresponding less electron-donating anilino derivative (NR^1_2 = NHPh) immediately cyclized (92KFZ62) (Scheme 56). In addition to the transformation to thienopyridines (**221**) the 2,4-bisalkylthiopyridines (**227**) (formed from **225, 226**) also allowed the annulation of a second thiophene ring by the Thorpe–Ziegler reaction, affording the bisthienopyridine **228** [92JCR(S)144] (Scheme 58).

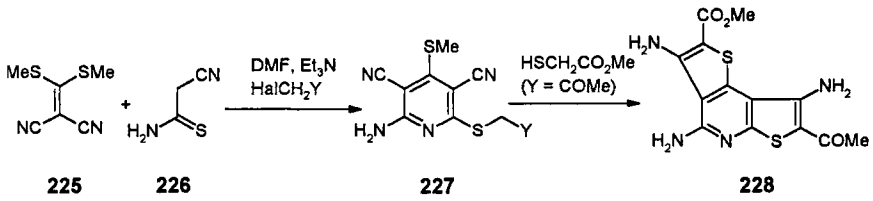
The formation of tetracyclic thiophene (**232**) (via **231**) by the Thorpe–Ziegler reaction in the presence of N-bromsuccinimide (NBS) represents a special case, because the pyrimidine-2-thione **229** also served as precursor for the CH-acidic alkylation agent **230** (95H2195) (Scheme 59).

The aminothiophene synthesis by the Thorpe–Ziegler cyclization (Scheme 53) could also be applied to the preparation of thienoquinolines (**234**) (from **233**) [86JHC925; 88JCR(S)50; 92CCC2359, 92PS219; 95SC451] and thienoisoquinolines (**235**) (84ZOR2442) (Scheme 60). The formation of N-substituted thieno[2,3-*b*]pyridines such as **237** were reported to be the result of the reaction of dimeric malodinitrile (**236**) with phenyl isothiocyanate and alkylating reagents such as ethyl chloroacetate (92M341) (Scheme 61). Similarly, by the formation of both a six-membered ring and a thiophene ring, the benzo-annulated N-substituted thienopyridinone **240** (91EUP416820), and the thienobenzodithiines **243** (84S854) were synthesized starting from methyl *o*-cyanomethylbenzoate (**238**) or the *o*-chlorophenylsulfone **241** (via **239, 242**), respectively (Scheme 61).



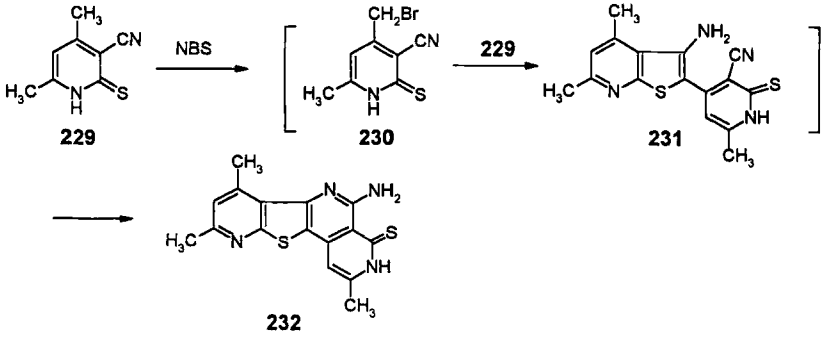
222 **223** **224**

SCHEME 57



225 **226** **227** **228**

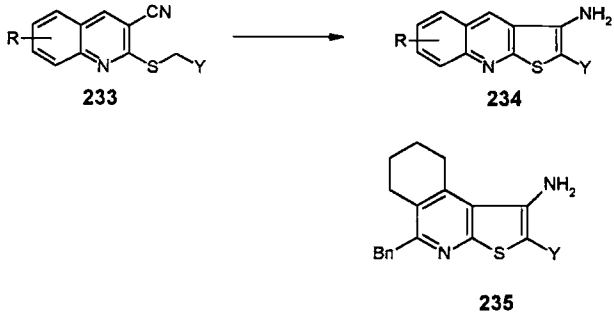
SCHEME 58



229 **230** **231**

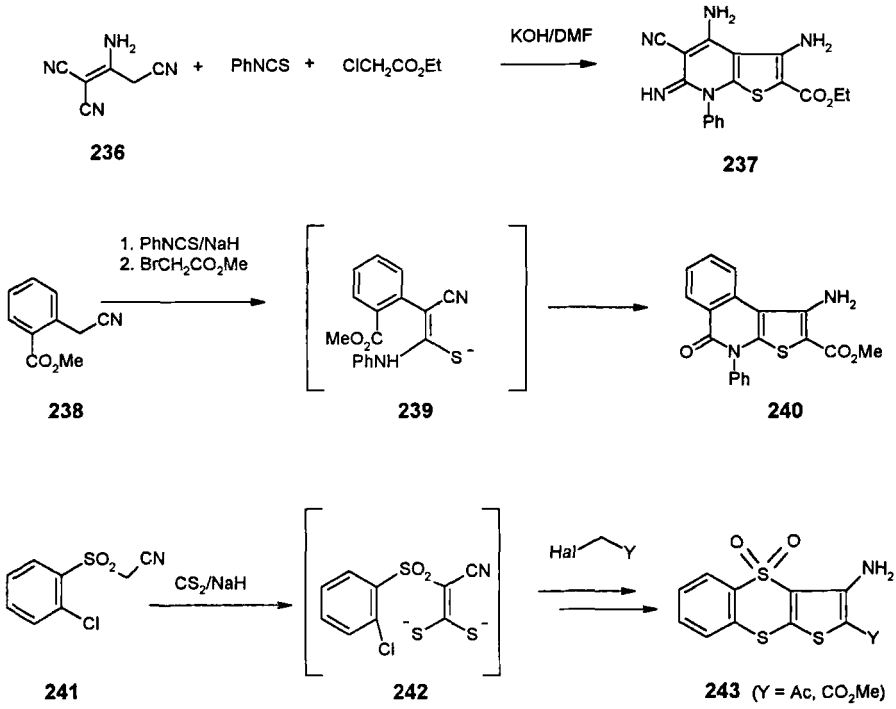
232

SCHEME 59



233 **234** **235**

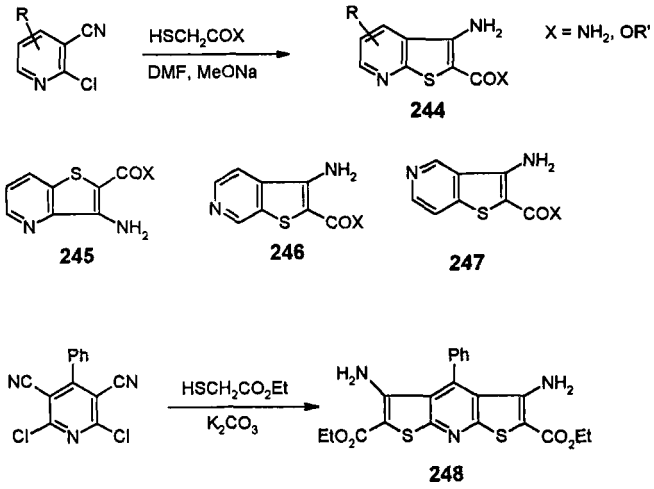
SCHEME 60



SCHEME 61

Another important route to thienopyridines with general structure **244** is based on the reaction of *o*-chlorocyanopyridines with thioglycolates [87JHC85; 91PHA415; 92IJC(B)492, 92JOC4179, 92JPR483; 94H1299; 96KFZ36]. In this way all the other isomeric thienopyridines (**245–247**) also were accessible (87JHC85) (Scheme 62). This method also allowed two thiophene rings (**248**) (94H1299) to be constructed when two *o*-chloronitrile units were present in the starting material (Scheme 62). Moreover, a 3-amino-2-phenylthieno[2,3-*c*]pyridine analogous to **246** was readily formed with benzylmercaptan in the presence of NaOEt in spite of the weak CH acidity of the benzylthio group (83T4153). Thienopyridines **244** and **246** could also be prepared from the corresponding bromocyanopyridines and ethyl thioglycolate under irradiation and in the presence of *t*-BuOK (83T4153).

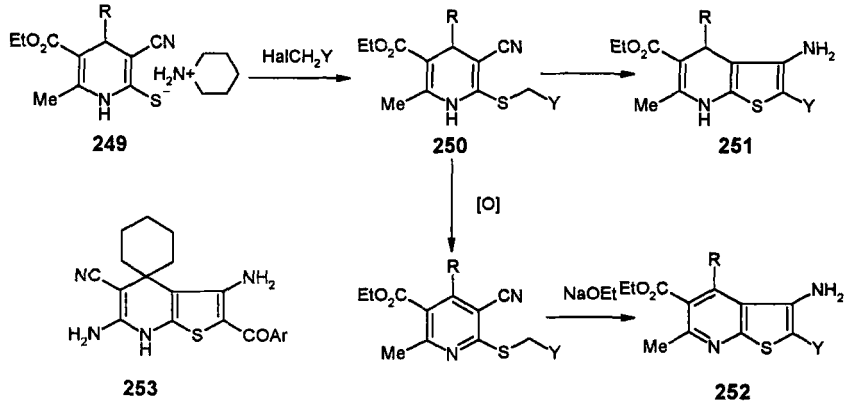
Thorpe–Ziegler cyclization was further applied to the 1,4-dihydropyridine series (87KGS124; 88ZOR460; 92KFZ40; 93DOK1597; 96KGS553) (see **249, 250**). Unless the 4-position is disubstituted as in the case of dihydropyridothiophene (**253**) (96IZV2535), there is the possibility that fully conjugated



SCHEME 62

thieno[2,3-*b*]pyridines (**252**) (87KGS124) are formed rather than the expected dihydro derivatives (**251**), due to the easy oxidation of **251** (Scheme 63).

By routes similar to those for thienopyridines, thieno[2,3-*d*]pyrimidines (**257**), thieno[2,3-*c*]pyridazines (**261**) (via **260**), and thienoquinoxalines (**265**) (via **264**) were synthesized via Thorpe–Ziegler cyclizations, starting materials include the *o*-cyanothiones **254** (via **256**) [84JCS(P1)2447; 91PS(60)223; 92KGS1280; 96T1011], **258** [90JPR104, 90MI3; 91M413, 91ZN(B)835; 94PS203], and **262** [91PS(61)151; 93PS(79)77], which are alkylated, or the *o*-chloronitriles



SCHEME 63

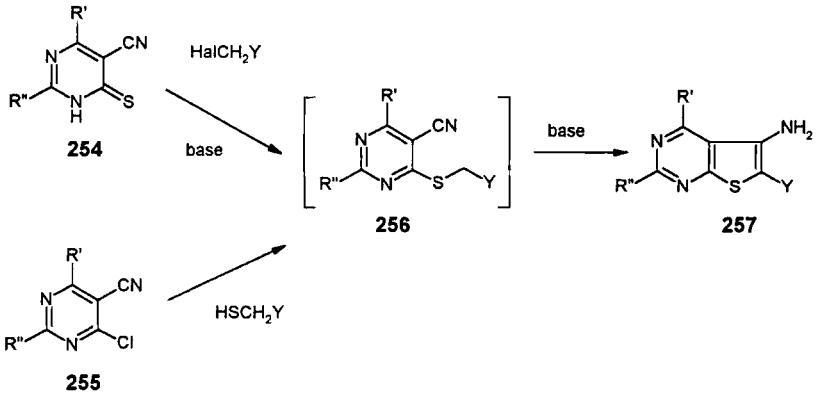
255 (87KGS1131; 88JHC959, 88KGS1559, 88LA633; 90JHC717), **259** [90JPR104, 90MI3; 91M413; 91ZN(B)835; 94PS203], and **263** [91PS(61)151; 93PS(79)77], which are substituted (Schemes 64–66). The thieno[2,3-*b*]pyrazine **266** (89JA285) could be obtained in a similar manner from the corresponding *o*-chloronitrile precursor (Scheme 67).

The formation of thieno[2,3-*d*]pyrimidine **269** (Scheme 68) does not follow general path of Scheme 64 because the Thorpe–Ziegler precursor **268** was generated by ring opening of the starting aminoisothiazole (**267**) in the presence of chloroacetone as alkylating reagent [88JCR(S)46].

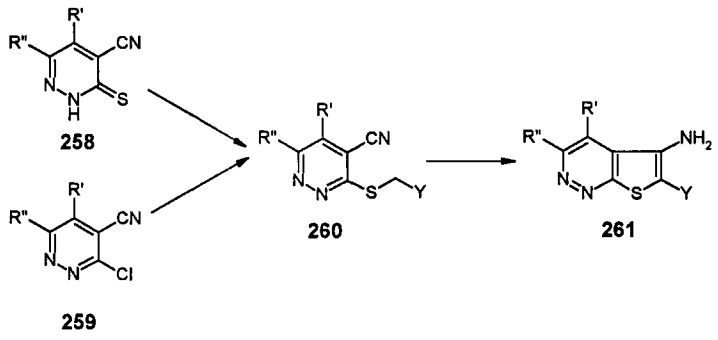
V. Synthesis of 3-Aminoselenophenes

2-Aminoselenophenes (**273**) were synthesized starting from β-chlorocinnamonitrile (**270**) by selenylation/alkylation and then Thorpe–Ziegler cyclization (92M455) of **272** (Scheme 69). The unstable 3-selenylcinnamonitrile **271** was not isolated.

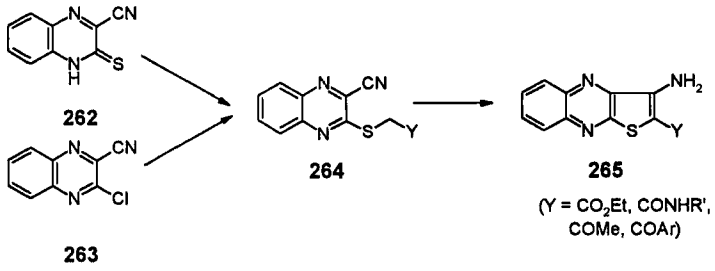
Pyridine-2-selenones (**274**) are more stable and served as precursors (via **275**) for selenopheno[2,3-*b*]pyridines (**276**) (84IZV2760, 84KGS708, 85S98, 85ZOB1656; 86IZV406; 88KPS138; 89CS327, 89ZOB881; 90ZOB2384, 90ZOB2750; 91ZOB747, 91ZOB942; 93PS(82)691; 94KGS122) (Scheme 70). The substituted methylselenopyridines are more prone to Thorpe–Ziegler cyclization than the corresponding methylthiopyridines (**220**) (94KGS122) (Scheme 56). The dihydroselenopheno[2,3-*b*]pyridine **277** was obtained in the same way (91ZOB948) (Scheme 70).



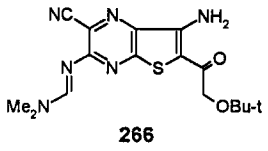
SCHEME 64



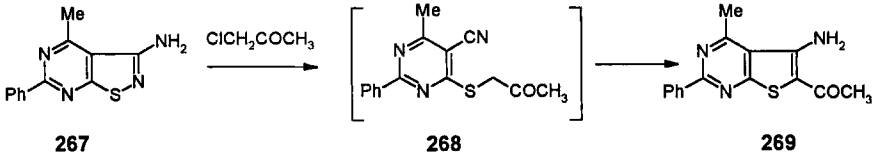
SCHEME 65



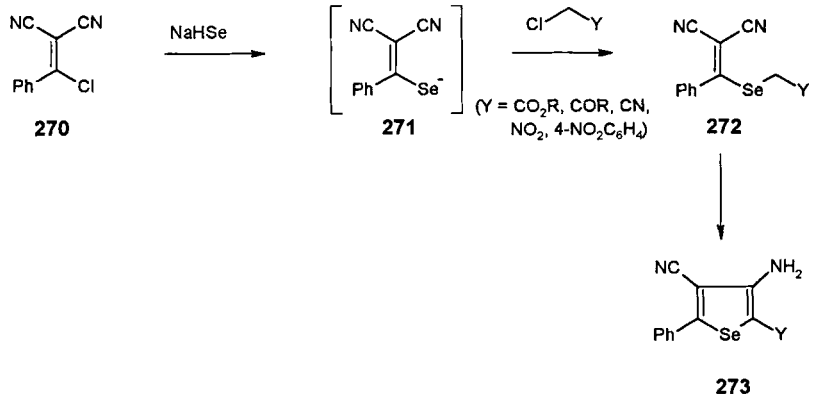
SCHEME 66



SCHEME 67



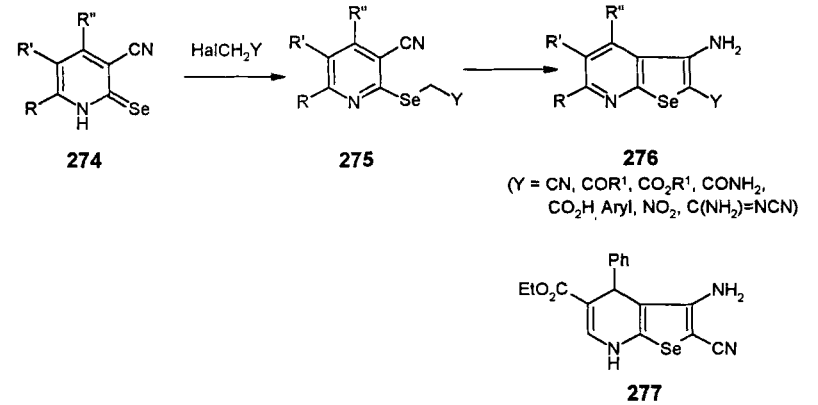
SCHEME 68



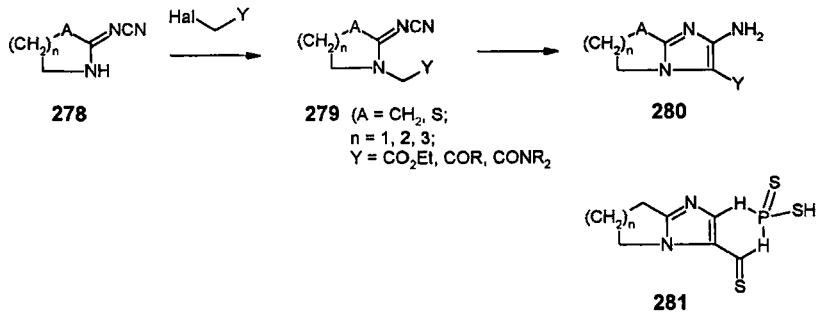
SCHEME 69

VI. Synthesis of Aminoazoles

Thorpe–Ziegler cyclization can also be applied to the synthesis of azoles (**1**) with X or Y as N atoms (see Scheme 1). The majority of known examples started with cyanamide derivatives **1** (X = N) and hence provided 1,3-azoles. Thus, semicyclic cyanamidine structures **278** could by alkylated at the ring N atom in the presence of a base (e. g., NaH), giving the Thorpe–Ziegler precursors **279** that led to the condensed aminoimidazoles **280** {A = CH (91LA975, 91KGS754), A = S [85JAP(K)60/28982, 85JAP(K)60/51194, 85JAP(K)60/51195; 88S261; 92KFZ62]} (Scheme 71). Imidazo-1,3,2-diaza-



SCHEME 70



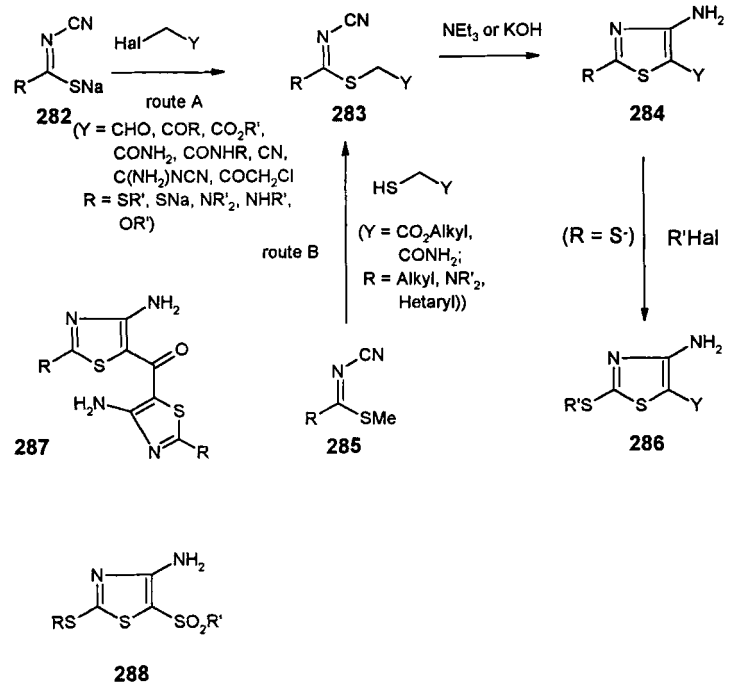
SCHEME 71

phosphorines (**281**) were obtained when intermediate amides (**279;** A = CH_2, Y = $CONH_2$) were treated with P_4S_{10} in pyridine (92KFZ63, 95MC67).

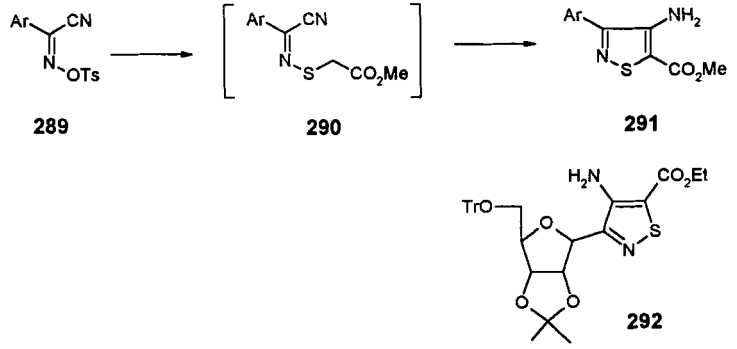
N-Cyanoisothioamide, precursors for the synthesis of 4-amino-1,3-thiazoles, are available by various routes. For example, *N*-cyanoisothioamides (**282**) were alkylated, giving **283** (route **A**) and, after cyclization, thiazoles (**284**) (83BCJ3851, 83JOC3340, 83ZC179; 84H697, 84JHC1361; 86JHC1435; 89EUP301613; 90MIP1; 91SL179; 95ZOR127; 96T1011) (Scheme 72). In the same manner bisaminothiazolylketones (**287**) could be obtained by a twofold Thorpe–Ziegler reaction using one equivalent of 1,3-dichloroacetone as the alkylating reagent (Y = $COCH_2Cl$) and two equivalents of **282** (86JHC1435). Sometimes no extra base was necessary for the synthesis of the thiazoles **284** according to route **A**. If cyanimidodithiocarbonates (**282;** R = SNa) were used, Thorpe–Ziegler cyclization to **284** was followed by *S*-alkylation, affording thiazoles **286** (84CCC2285). Sulfones (**288**) were obtained from the corresponding *S*-chloromethyl-*N*-cyanoisothioamides (**283;** Y = Cl) by nucleophilic substitution with $R'SO_2Na$ and Thorpe–Ziegler cyclization (89EGP253424).

Alternatively, 4-amino-1,3-thiazoles (**284**) could be by synthesized according to route **B,** on substitution of the methylthio group in *S*-methylisothioamides **285** by α-mercaptocarbonyl compounds (86LA780; 87S940; 95G115) (Scheme 72). Thorpe–Ziegler cyclization of thiooximes (**290**) of acylcyanides gave access to 4-aminoisothiazoles such as **291** (82EUP48615) (Scheme 73). The former were obtained from the corresponding *O*-tosyloximes (**289**) and mercaptoacetate. In the same manner the *C*-glycoside **292** was obtained (93JOC5181).

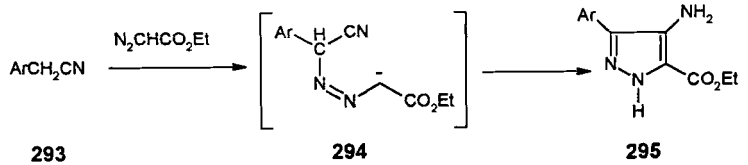
The interaction of ethyl diazoacetate with benzylcyanides (**293**) opened a straightforward way to aminopyrazoles (**295**) (84FES618), probably via azo intermediates **294** (Scheme 74).



SCHEME 72



SCHEME 73



SCHEME 74

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